

# **EXHIBIT 14**

# Letters

## RESEARCH LETTER

### Postincarceration Fatal Overdoses After Implementing Medications for Addiction Treatment in a Statewide Correctional System

As the epidemic of opioid use in the United States continues to shift from prescription opioids to illicit drugs,<sup>1</sup> more people living with opioid use disorder are encountering the criminal justice system. Most US correctional facilities do not continue or initiate medications for addiction treatment (MAT).<sup>2</sup> This is especially unfortunate given the higher rates of opioid overdose immediately after release from incarceration.<sup>3</sup>

In July 2016, a new model of screening and protocolized treatment with MAT (including methadone, buprenorphine, or naltrexone) launched at the Rhode Island Department of Corrections (RIDOC), a unified prison/jail. A community vendor with statewide capacity to provide MAT after release was engaged to help run the program in November 2016, and all sites were operational by January 2017. Individuals arriving into RIDOC while receiving MAT were to be maintained on their respective medications regimen without tapering or discontinuing their medications. Contemporaneously, a system of 12 community-located Centers of Excellence in MAT was established to promote transitions and referrals of inmates released from RIDOC. This analysis examines preliminary association of the program with overall overdose fatalities and deaths from overdose among those individuals who were recently incarcerated.

**Methods** | We conducted a retrospective cohort analysis linking data from the Rhode Island Office of State Medical Examiners for all unintentional deaths from overdose occurring from January 1 to June 30, 2016, and from January 1 to June 30, 2017, to data from RIDOC inmate releases. Decedents were defined as individuals who were recently incarcerated if they died within 12 months of release from RIDOC. Descriptive statistics of decedents include summarized demographics, the status of incarceration, and the number of fentanyl-related overdoses. Aggregate data of inmates released from RIDOC, counts of naloxone provided to inmates after release, and the monthly receipt of MAT were also reported. Risk ratios (RRs) and 95% CIs were used to compare the proportion of decedents who were recently incarcerated in 2017 with those who were incarcerated in 2016, since individual-level MAT program enrollment data were unavailable. The number needed to treat was estimated from the risk difference of recent incarceration between the 2 periods.  $\chi^2$  Tests compared differences in decedent characteristics between 2016 and 2017. Statistical analysis was performed using SAS program, version 9.3 (SAS Institute Inc) with 2-sided  $P < .05$  considered statistically significant. The Rhode Island Hospital institutional review board approved this protocol with a waiver of written informed consent.

**Results** | Statewide in Rhode Island, there were 179 overdose deaths from January 1, 2016, to June 30, 2016, compared with 157 overdose deaths during the same period in 2017, a reduc-

Table 1. Characteristics and Number of Deaths From Accidental Overdose in Rhode Island, Both Overall and Among Individuals With Recent Incarceration<sup>a</sup>

Characteristic	Decedents With Recent Incarceration, No. (%)		Overall No. of Decedents (%)	
	First 6 mo of 2016 (n = 26)	First 6 mo of 2017 (n = 9)	First 6 mo of 2016 (n = 179)	First 6 mo of 2017 (n = 157)
Sex				
Male	24 (92.3)	7 (77.8)	123 (68.7)	94 (59.9)
Female	2 (7.7)	2 (22.2)	56 (31.3)	63 (40.1)
Race/ethnicity <sup>b</sup>				
White	25 (96.2)	8 (88.9)	168 (93.9)	137 (87.3) <sup>c</sup>
Other	1 (3.8)	1 (11.1)	11 (6.1)	20 (12.7)
Age, y				
18-29	8 (30.8)	2 (22.2)	43 (24.0)	23 (14.6) <sup>d</sup>
30-39	9 (34.6)	4 (44.4)	34 (19.0)	54 (34.4)
40-49	6 (23.1)	3 (33.3)	40 (22.3)	35 (22.3)
≥50	3 (11.5)	0 (0.0)	62 (34.6)	45 (28.7)
Died of overdose attributed to fentanyl	16 (61.5)	8 (88.9)	92 (51.4)	92 (58.6)
Length of incarceration, median (IQR), mo	30 (4-70)	23 (9-113)	NA	NA
Time since release from incarceration to death, median (IQR), d	112 (12-223)	190 (49-241)	NA	NA
Died within 30 d of release from incarceration	10 (38.5)	1 (11.1)	NA	NA

Abbreviations: IQR, interquartile range; NA, not applicable.

<sup>a</sup> Recent incarceration was defined as within 12 months of release from the Rhode Island Department of Corrections.

<sup>b</sup> Race as recorded by the Rhode Island Office of State Medical Examiners at the time of autopsy or case review.

<sup>c</sup>  $\chi^2$  Test comparing all decedents, January 1 to June 30, 2016, vs January 1 to June 30, 2017,  $P = .04$ .

<sup>d</sup>  $\chi^2$  Test comparing all decedents, January 1 to June 30, 2016, vs January 1 to June 30, 2017,  $P = .007$ .

**Table 2. Characteristics of Individuals Incarcerated in Rhode Island From January 1 to June 30, 2016, and From January 1 to June 30, 2017**

Characteristic	First 6 mo of 2016	First 6 mo of 2017
Admission for incarceration, No.	4822	4512
Release from incarceration, No.	4005	3426
No. of inmates receiving MAT monthly, mean (SD)	80 (18) <sup>a</sup>	303 (39)
No. of inmates receiving a specific MAT drug monthly, mean (SD)		
Buprenorphine	4 (3)	119 (15)
Methadone	74 (16)	180 (25)
Naltrexone	2 (1)	4 (1)
Naloxone kits dispensed at release from incarceration, No.	72	35

Abbreviations: MAT, medications for addiction treatment; RIDOC, Rhode Island Department of Corrections.

<sup>a</sup> Some medications for treatment of addiction were in use at RIDOC in specialized circumstances. Treatment with an opioid agonist is standard of care for pregnant women with opioid use disorder. Pregnant women with opioid use disorder incarcerated at RIDOC are typically treated with methadone and less frequently with buprenorphine. A pilot study providing naltrexone by injection had been ongoing since December 2015 prior to the start of the MAT program at RIDOC.

tion of 12.3%. Characteristics of decedents included in the 2017 group were generally comparable with those of decedents in 2016, but the 2017 group was slightly older and less likely to be of white race/ethnicity (Table 1). Most deaths from overdose were fentanyl-related. For decedents who were recently incarcerated, there were no statistically significant differences in characteristics of those decedents in 2016 vs 2017. The total number of admissions and releases from incarceration were similar over time; however, the provision of naloxone to inmates after release from incarceration declined, and the monthly receipt of MAT after release from incarceration increased (Table 2).

In the 2016 period, 26 of 179 individuals (14.5%) who died of an overdose were recently incarcerated compared with 9 of 157 individuals (5.7%) in the 2017 period, representing a 60.5% reduction in mortality (RR, 0.4; 95% CI, 18.4%-80.9%;  $P = .01$ ). The number needed to treat to prevent a death from overdose was 11 (95% CI, 7-43).

**Discussion** | We observed a large and clinically meaningful reduction in postincarceration deaths from overdose among inmates released from incarceration after implementation of a comprehensive MAT program in a statewide correctional facility—a reduction contributing to overall population-level declines in overdose deaths. Results are consistent with other studies of the provision of MAT during incarceration,<sup>4</sup> yet it is remarkable that the reduction in mortality occurred in the face of a devastating, illicit, fentanyl-driven overdose epidemic.<sup>5,6</sup> Alternative explanations for the observed reductions (eg, differences in population or the provision of naloxone) linked to recent incarceration are unsupported.

Limitations of this study include a small sample size, a lack of MAT data after inmate release, and possible misclassification of program exposure (eg, refusal of MAT, denial of opioid use disorder, and staggered MAT program implementation), which may have underestimated the association. Additional individual-level and longitudinal analyses are warranted.

Identification and treatment of opioid use disorder in criminal justice settings with a linkage to medication and supportive care after release from incarceration is a promising strategy to rapidly address the high rates of overdose and opioid use disorder in the community.

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**Study concept and design:** Green, Clarke, Boss, Rich.

**Acquisition, analysis, or interpretation of data:** Green, Clarke, Brinkley-Rubinstein, Marshall, Alexander-Scott, Rich.

**Drafting of the manuscript:** Green, Brinkley-Rubinstein, Marshall, Boss.

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**Obtained funding:** Brinkley-Rubinstein, Rich

**Administrative, technical, or material support:** Green, Clarke, Brinkley-Rubinstein, Alexander-Scott, Boss, Rich.

**Study supervision:** Green, Marshall, Alexander-Scott, Rich.

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1. O'Donnell JK, Halpin J, Mattson CL, Goldberger BA, Gladden RM. Deaths involving fentanyl, fentanyl analogs, and U-47700—10 states, July–December 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66(43):1197-1202.

2. Nunn A, Zaller N, Dickman S, Trimbur C, Nijhawan A, Rich JD. Methadone and buprenorphine prescribing and referral practices in US prison systems: results from a nationwide survey. *Drug Alcohol Depend.* 2009;105(1-2):83-88.
3. Merrall EL, Kariminia A, Binswanger IA, et al. Meta-analysis of drug-related deaths soon after release from prison. *Addiction.* 2010;105(9):1545-1554.
4. Marsden J, Stillwell G, Jones H, et al. Does exposure to opioid substitution treatment in prison reduce the risk of death after release? a national prospective observational study in England. *Addiction.* 2017;112(8):1408-1418.
5. Carroll JJ, Marshall BDL, Rich JD, Green TC. Exposure to fentanyl-contaminated heroin and overdose risk among illicit opioid users in Rhode Island: a mixed methods study. *Int J Drug Policy.* 2017;46:136-145.
6. Marshall BDL, Krieger MS, Yedinak JL, et al. Epidemiology of fentanyl-involved drug overdose deaths: a geospatial retrospective study in Rhode Island, USA. *Int J Drug Policy.* 2017;46:130-135.

## COMMENT & RESPONSE

### Mendelian Randomization Concerns

**To the Editor** With interest we read the article by Hartwig et al.<sup>1</sup> The authors used 2-sample mendelian randomization<sup>2</sup> to investigate the role of C-reactive protein (CRP) in schizophrenia. Their main finding listed in the abstract and body is a pooled odds ratio estimate of 0.9 (random effects 95% CI, 0.84-0.97;  $P = .005$ ) per 2-fold increment in CRP levels in their inverse variance-weighted random-effects model.

First, by comparing the input CRP-associated single-nucleotide polymorphism (SNP) data from the original CRP genome-wide study<sup>3</sup> (see eTable 2 in the Supplement by Hartwig et al<sup>1</sup>), it came to our attention that the effect allele at rs9987289, the only variant “classified as influential,”<sup>1</sup> differs between the studies by Hartwig et al<sup>1</sup> and Dehghan et al.<sup>3</sup> We invite the authors to comment on their choosing the G allele as the effect allele instead of using the data in Table 2 of Dehghan et al.<sup>3</sup>

Second, the authors refer to a study by Prins et al<sup>4</sup> in which mendelian randomization analyses were performed using genetic risk scores of liberal CRP-associated SNPs as instrumental variables also in schizophrenia. These genetic risk scores are derived from the original CRP study,<sup>3</sup> the same data resource Hartwig et al<sup>1</sup> used. Both groups extracted 18 SNPs. Prins et al<sup>4</sup> did not extract 3 SNPs from Psychiatric Genomics Consortium schizophrenia summary statistics, resulting in 15 SNPs for their actual analyses. Aiming to elucidate the true effect size for CRP-associated SNPs in risk for schizophrenia, we tried to replicate both articles’ findings. To that end, we applied our own scripts ([https://github.com/Bochao1/MR\\_CRP\\_SCZ](https://github.com/Bochao1/MR_CRP_SCZ)) and the R packages TwoSampleMR and MendelianRandomization to perform the same inverse variance-weighted random-effects model as used by Hartwig et al<sup>1</sup> for their main finding, as well as 3 of their 4 other models. To get odds ratio estimates for schizophrenia per 2-fold CRP increments, we used the same equation<sup>1</sup> as follows:

$$(\sqrt{\text{OR}})^2$$

However, neither when considering G at rs9987289 as the effect allele nor when considering A as the effect allele did we obtain equal inverse variance-weighted random-effects results to Hartwig et al<sup>1</sup> (odds ratio, 0.90 per 2-fold CRP incre-

ment; 95% CI, 0.85-0.96;  $P = .001$ ; and odds ratio, 0.93; 95% CI, 0.86-0.99;  $P = .030$ , respectively).<sup>5</sup>

Our findings hint that the actual effect size for CRP-associated SNPs to increase risk of schizophrenia may differ from the findings of Hartwig et al.<sup>1</sup> To improve future replication opportunities, we propose that authors refer to publicly accessible statistical analysis codes (eg, <https://github.com/>) and R packages and outline their data extraction procedures.

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**Conflict of Interest Disclosures:** None reported.

1. Hartwig FP, Borges MC, Horta BL, Bowden J, Davey Smith G. Inflammatory biomarkers and risk of schizophrenia: a 2-sample mendelian randomization study. *JAMA Psychiatry.* 2017;74(12):1226-1233.

2. Hartwig FP, Davies NM, Hemani G, Davey Smith G. Two-sample mendelian randomization: avoiding the downsides of a powerful, widely applicable but potentially fallible technique. *Int J Epidemiol.* 2016;45(6):1717-1726.

3. Dehghan A, Dupuis J, Barbalic M, et al. Meta-analysis of genome-wide association studies in >80 000 subjects identifies multiple loci for C-reactive protein levels. *Circulation.* 2011;123(7):731-738.

4. Prins BP, Abbasi A, Wong A, et al; PAGE Consortium; International Stroke Genetics Consortium; Systemic Sclerosis consortium; Treat OA consortium; DIAGRAM Consortium; CARDIOGRAMplusC4D Consortium; ALS consortium; International Parkinson's Disease Genomics Consortium; Autism Spectrum Disorder Working Group of the Psychiatric Genomics Consortium; CKDGen consortium; GERAD1 Consortium; International Consortium for Blood Pressure; Schizophrenia Working Group of the Psychiatric Genomics Consortium; Inflammation Working Group of the CHARGE Consortium; Investigating the causal relationship of c-reactive protein with 32 complex somatic and psychiatric outcomes: a large-scale cross-consortium mendelian randomization study. *PLoS Med.* 2016;13(6):e1001976.

5. GitHub. Bochao1/MR\_CRP\_SCZ: replicate study for Prins et al and Hartwig et al. [https://github.com/Bochao1/MR\\_CRP\\_SCZ](https://github.com/Bochao1/MR_CRP_SCZ). Accessed February 7, 2018.

**In Reply** The comments by Lin et al on our mendelian randomization analysis of the association of circulating C-reactive protein (CRP) with schizophrenia risk<sup>1</sup> indicate their concern over the proper extraction and harmonization of data within 2-sample mendelian randomization studies. We agree that this is an important topic<sup>2</sup> that is vital for ensuring the reproducibility and reliability of scientific findings, and we appreciate the opportunity to provide some clarifications.

Specifically, they questioned why we considered the G allele, rather than the A allele, as the effect allele for the rs9987289 variant (one of the CRP instruments). It is true that the A allele was indicated as the effect allele in Table 2 of the study by Dehghan et al,<sup>3</sup> which shows summary association results for the replication and discovery plus replication stages.

Table 1 in the study by Dehghan et al<sup>3</sup> indicates that the G allele was the effect allele in the discovery stage. They reported